#18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U. S. Patent: 4,224,946
Issued: September 30, 1980

Assignee: American Cyanamid Company
Inventor: Donald S. Kaplan
Group: 120

Serial No.: 933,224
Filed: August 14, 1978
Director: Charles E. Van Horn

Title: SURGICAL SUTURES DERIVED FROM SEGMENTED POLYETHER-ESTER BLOCK COPOLYMERS

November 18, 1985

Hon. Commissioner of Patents
and Trademarks

Washington, D.C. 20231

S i r:

Application For Extension
Of The Term Of U.S. Patent 4,224,946

This application, filed in duplicate, is respectfully submitted in compliance with 35 U.S. Code 156, Extension of Patent Term. It is certified that the duplicate application is identical to the original application. An extension of the term of U.S. patent 4,224,946 covering the "approved product" (as defined hereinafter) is respectfully requested.

Applicant has determined and submits that U.S. Patent No. 4,224,946 is subject to, and meets the conditions for, extension of its term in compliance with the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 USC 156, published in 1047 OG 16-20 (1984), part A sections (a)-(b) and part B sections (a)-(g), and that this application for extension is being submitted in compliance with part C thereof.

The claims 1, 4 and 5 of U.S. patent 4,224,946 (hereinafter '946 patent) are currently the subject of a civil litigation in the U.S. District Court for the District of New Jersey, Civil Action No. 85-3053 (MTB), filed June 19, 1985. This litigation was initiated from a decision of the U.S. Patent and Trademark Office (hereafter PTO) Board of Patent Appeals and Interferences dated April 23, 1985 (Interference No. 100,952) awarding the priority of these claims to a U.S. patent application assigned to

ST-52 11/79

Ethicon, Inc., Sommerville, New Jersey (Ethicon). A copy of the litigation particulars is attached to this application and identified as Appendix A.

No decision has been received to date on this litigation, however, there is the possibility that the District Court will affirm the PTO and award claims 1, 4 and 5 of the '946 patent to Ethicon. Such a decision may prevent applicant from extending the term of the '946 patent and in obtaining the benefit of Section 156. In order to avoid such a situation, applicant has filed a "substitute" application concurrently herewith for the extension of applicant's U.S. patent 4,246,904 which also covers the "approved product", but is not involved in any litigation. It is to be clearly understood, however, that applicant is not trying to obtain the extension of two patents for the same "approved product".

What applicant is requesting is that applicant first and only be granted an extension of the term of the '946 patent should applicant prevail in the litigation, and second that applicant only be granted an extension of the term of the '904 patent should applicant not prevail in the litigation. What applicant is trying to avoid is the loss of any rights to extending a patent covering applicant's "approved product".

The following paragraph numbers correspond to those in the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 USC 156, part D section(b), which guidelines have been published in 1047 OG 16-20 (1984).

(1) The approved product is a monofilament non-absorbable polybutester surgical suture. The approved product is marketed in the U.S. under the trademark Novafil® (American Cyanamid Company), either clear or tinted blue. The approved product is indicated for use in all types of soft tissue approximation, including use in cardiovasuclar and ophthalmic surgery, but not in microsurgery and neural tissue. It is recommended for

use where the possibility of reduced suture reaction is desired.

The blue NOVAFIL® suture is tinted with [phthalocyaninato (2-)] copper.

The NOVAFIL® suture is available either non-needled or affixed to various ATRAUMATIC® and D-TACH® (both American Cyanamid Company trademarks) needles.

Sterile packages are available in U.S. Pharmacopeia (hereafter USP) sizes 10/0 through 02 (metric size 0.2-5) for blue, and 7/0 through 02 (metric size 0.5-5) for clear sutures.

(2) The Federal statute under which the regulatory review occurred is the U. S. Code (hereafter USC) Title 21 - Food and Drugs; Chapter 9 - Federal Food, Drug, And Cosmetic Act; Section 360e - Premarket Approval; Subsection (d) - Action On An Application For Premarket Approval.

(3) The approved product, identified in paragraph (1) above, received permission for commercial marketing on September 30, 1985.

(4) This application is being submitted within the sixty day period permitted under 35 USC 156. The last day of the sixty day period is November 29, 1985.

(5) A complete identification of the '946 patent is in the heading of this application.

(6) A copy of the patent, in the form of a cut-up copy, is attached to this application and is identified as Appendix B.

(7) A copy of the (only) certificate of correction in the '946 patent is attached to this application and identified as Appendix C. No disclaimer has been made in this patent.

No maintenance fees are due on the '946 patent (the patent application was filed before December 12, 1980, which is the earliest filing date for maintaining an issued U.S. patent). Please see 37 CFR 1.20, Post-issuance fees.

No reexamination certificate has issued on the '946 patent. The assignee has not filed a request, and has no knowledge of a third party filing a request for reexamination.

(8) All of the claims (1 to 7) in columns 6 to 8 of Appendix B describe the approved product discussed in paragraph (1) above. The manner in which each patent claim reads on the approved product is shown in attached Appendix D.

In Appendix D, the pages numbered 1 to 3 (with page 1 containing the heading "DEVICE CHARACTERISTICS") were submitted to the Food and Drug Administration as part of the Premarket Approved Application, Section VII. Page 3 has been supplemented for purposes of the claim comparison.

The September 30, 1985 letter from the Food and Drug Administration is a notification of the PMA approval. The letter has been excerpted to specifically show the approval of a needled suture and a sterile package containing the suture.

(9) The relevant dates and information pursuant to 35 USC 156(g) are: Investigational Drug Exemption (hereafter IDE)-approved on April 30, 1982; Premarket Approval (hereafter PMA) application - filed on September 14, 1984; and PMA application - approved on September 30, 1985.

(10) The activities undertaken by the '946 patent assignee during the regulatory review period, defined by the dates in paragraph (9) above, are discussed in the PMA Application, Comprehensive Summary, Part III, Sections E, Summary of Studies and F, Clinical Studies. A copy of pages 3 to 9 inclusive of the Comprehensive Summary which describe Sections E and F are attached to this application and identified as Appendix E.

The significant dates applicable to the studies described in Appendix E are given in paragraph (9) above, plus the following: A request for an IDE was filed on March 31, 1982.

(11) It is the assignee's opinion that all the claims of the '146 patent are eligible for a patent extension of 626 days. The length of extension was determined by the following calculations:

(a) IDE Approval to PMA Application

	Days
April 30, 1982 (IDE approval) to December 31, 1982:	246
plus	
January 1 to December 31,1983:	365
plus	
January 1 to PMA filing on September 14, 1984 (a leap year)	258
Total	869
(b) PMA Application to Approval	
September 14 (PMA filing) to December 31, 1984:	109
plus	
January 1 to PMA approval on September 30, 1985:	273
Total	382
(c) Regulatory Review Period: 869 + 382 days = Grand Total	1251
(d) Extension = $\frac{1251}{2}$ =	626

(12) The assignee acknowledges the duty to disclose to the Commissioner of Patents & Trademarks and the Secretary of Health and Human Services any information which is material to any determination relating to this patent extension application. It is respectfully submitted that the assignee has met this duty by the information contained in this application, which includes the attached appendices.

(13) The Commissioner is authorized to debit the assignee's PTO deposit account No. 01-1300 for any prescribed fees related to the receiving and/or acting upon this application.

A declaration signed by an Agent of the assignee is attached to this application and is identified as appendix F. In summary, the declaration states that the assignee believes the '946 patent is entitled to an extension of 626 days, under the provisions of 35 U.S. Code 156.

CONCLUSION

It is respectfully submitted that this application is in order and that the assignee is entitled to an extension of 626 days. A timely notice of this extension by the Patent &

Trademark Office is respectfully requested and will be greatly appreciated.

If the director has any questions relating to this application, or needs aditional information or clarification, a telephone contact to the assignee's attorneys, Messrs. J. W. Richards, Telephone No. (203) 348-7331 (Ext. 2413) or C. F. Costello, Jr. (Ext. 2333), is invited.

John J. Hagan
Manager
Patent Law Department
Registration No. 17,129

Attachment
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APPENDIX A

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July 12, 1985

REGISTERED MAIL

Nannle D. Henry
Deputy Clerk, Board of Patent Appeals
and Interferences
Box Interference
Commissioner of Patents and Trademarks
Washington, D. C. 20231

Re: Interference No. 100,952, Gertzman, et al v. Kaplan

Dear Sir:

This notice is submitted on behalf of American Cyanamid Company, assignee of the senior party, Samuel Kaplan, in the above-entitled interference.

Please take notice that American Cyanamid Company has filed a civil action pursuant to 35 U.S.C. §146, seeking a determination awarding its assignor, Kaplan, priority in the subject matter of the Interference Counts, and for other relief. The action was filed on June 19, 1985 in The United States District Court for The District of New Jersey and is styled American Cyanamid Company v. Ethicon, Inc., Civil action No. 85-3053.

Very truly yours,

Richard G. Greco

RGG:bl

APPENDIX B 4,224,946

United States Patent [19]

Kaplan

[54] SURGICAL SUTURES DERIVED FROM SEGMENTED POLYETHER-ESTER BLOCK COPOLYMERS

[75] Inventor: **Donald S. Kaplan**, Ridgefield, Conn.

[73] Assignee: **American Cyanamid Company**, Stamford, Conn.

[21] Appl. No.: **933,224**

[22] Filed: **Aug. 14, 1978**

[51] **Int. Cl.**[3] **A61L 17/00**

[52] **U.S. Cl.** **128/335.5**

[58] **Field of Search** 128/335.5; 260/860; 206/63.3

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,359,983	12/1967	Northey	128/335.5
3,652,713	3/1972	Okazaki	260/860
3,766,146	10/1973	Witsiepe	260/860
3,784,520	1/1974	Hoeschele	260/860

3,861,521	1/1975	Burtz	128/335.5
3,875,946	4/1975	Duncan	128/335.5

FOREIGN PATENT DOCUMENTS

2265294 4/1977 Fed. Rep. of Germany .

OTHER PUBLICATIONS

J. Polymer Science, vol. XIV, pp. 15-28, (1954), Colcman.

J. Polymer Science, Symposium No. 48, pp. 47-60, (1974), Buck et al.

Primary Examiner—C. Fred Rosenbaum
Attorney, Agent, or Firm—Charles F. Costello, Jr.

[57] ABSTRACT

A synthetic nonabsorbable surgical suture compound of segmented polyether-ester block copolymers is disclosed.

7 Claims, No Drawings

SURGICAL SUTURES DERIVED FROM SEGMENTED POLYETHER-ESTER BLOCK COPOLYMERS

BACKGROUND OF THE INVENTION

This invention relates to a surgical suture composed of block polyether-esters which contain (1) a polymeric block of polyalkene esters and (2) a polymeric block of aromatic dicarboxylic acids or cycloaliphatic acids with short chain aliphatic or cycloaliphatic diols. This surgical suture can be a monofilament, or a twisted or braided multifilament article.

The medical profession is continuously seeking more satisfactory sutures to be used in closing wounds, whether such wounds are incisions from operations, or tears, cuts or abrasions from accidental or other causes. Many materials have been suggested for use as sutures. Sutures are divided into two board classes, the absorbable sutures, such as catgut or polyglycolic acid sutures, which are absorbed by the body tissues, and nonabsorbable sutures which either remain in the tissues in substantially their original form for prolonged periods or are removed from the skin surfaces after the underlying tissues have been healed. For nonabsorbable sutures many materials have been suggested which range from cotton and silk through various synthetic filaments such as polypropylene to stainless steel or nickel or other metallic filaments.

Other things being equal, the medical profession usually prefers the suture which is strongest. In spite of many disadvantages stainless steel has met with considerable acceptance because of its extremely high tensile strength. Such plastic materials as polypropylene are meeting currently with considerable commercial acceptance because of comparatively high tensile strength and because of other advantages over stainless steel.

Additionally, the suture material needs good handling characteristics. The handling characteristics of a suture, as a general statement, are difficult to define but should include a high degree of flexibility.

Handling characteristics include knot strength and knot security. That is, the suture must have such characteristics that a knot can be tied in the suture. Some materials are so brittle that if a suture made from them is knotted, the strength of the suture is markedly reduced. For some materials an overhand knot in a strand can reduce the strength of the strand by a factor of two or more. In addition to knot strength, the suture should have such characteristics that the knot when tied remains in position. Also, the suture should be "throwable" so that when the free end is placed in position by the surgeon it will remain in that position until moved. Similarly, the suture should have such characteristics that it can be thrown or moved from side to side and yet retain the position into which it is thrown.

A surgical suture comprising a high degree of tensile strength with a high degree of flexibility is therefore needed in the medical profession.

A polypropylene monofilament suture is one attempt at solving this need. The tensile strength of this suture is good when compared to stainless steel; and the flexibility of the suture, though better than stainless steel, is still considered to be stiff and springy. See, e.g., U.S. Pat. No. 3,630,205 which is incorporated herein by reference.

A polyurethane suture is another attempt. The primary advantage of this suture is its very high degree of

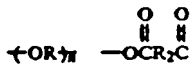
flexibility. However, this has low tensile strength and extremely high elongations at break which make it unsatisfactory for general wound closure methods. See, e.g., U.S. Pat. No. 3,454,011 which is incorporated herein by reference.

Other attempts include the braiding of materials with a high tensile strength but a low degree of flexibility. Dacron ® is an example of a suture with a satisfactory tensile strength after braiding and an increased degree of flexibility. A monofilament suture is generally preferred in most surgical procedures to a braided suture because of the reduced tissue drag of the monofilament. Also, in skin suturing a monofilament suture is generally preferred because it is usually less susceptible to capillary action than a braided suture.

This invention has advantages over these prior art attempts. The suture of this invention shows excellant strength and flexibility as a monofilament. Specifically, the surgical suture of this invention combines the tensile strength of a suture such as a polypropylene monofilament suture, with the flexibility of a braided or polyurethane suture.

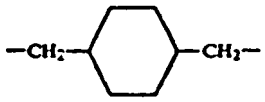
SUMMARY OF THE INVENTION

The discovery has now been made that a non-absorbable monofilament sterile surgical suture or ligature is comprised of a polymeric block (A) consisting of a polyalkylene ether of the formula



having a number average molecular weight of from about 500-3000 wherein R is a straight or branched chain alkyl group of from about 2 to 10 carbon atoms and R_2 is 1,4-phenylene or cyclohexylene and n is the number of repeating units; and a polymeric block (B) which is the reaction product of an aromatic dicarboxylic acid or a cycloaliphatic acid, and a short chain aliphatic or cycloaliphatic diol, having the formula

wherein R_1 is a straight or branched chain alkyl group of from about 2 to 10 carbon atoms or a cyclic group having the formula



and R_2 is 1,4-phenylene or cyclohexylene; and the block (B) comprising from about 30% to 95% of the copolymer. The copolymer has a number average molecular weight of from about 25,000 to 30,000. This suture has good flexibility, good fatigue life and high tensile strength.

The surgical suture or ligature wherein the polymeric block (B) comprises from about 55% to 80% of the copolymer is most preferred.

The surgical suture or ligature described above wherein R is selected from the group consisting of eth-

ylene, propylene or butylene is also preferred, and where R is butylene is most preferred.

Within the scope of this invention is the surgical suture or ligature described above having an attached needle.

The non-absorbable monofilament sterile surgical suture or ligature described above has approximately the following characteristics:

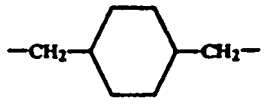
Straight Pull, pounds per square inch	At least about 50,000
Knot Pull, pounds per square inch	At least about 35,000
Flexual Modulus, pounds per square inch	Less than about 3.5×10^5
Flexual Fatigue, cycles to failure	At least about 1,000
Elongation at break, percent	Less than about 100%
Draw ratio	Between about 5× and 10×

The surgical suture wherein the Elongation at break percent is between about 25 and 55 is preferred.

Within the scope of this invention is a surgical suture package comprising a sterile enclosure and therein a non-absorbable monofilament sterile surgical suture or ligature described above comprising a polymeric block (A) consisting of a polyalkylene ether of the formula

having a number average molecular weight of from about 500-3000 wherein R is a straight or branched chain alkyl group of from about 2 to 10 carbon atoms and R_2 is 1,4-phenylene or cyclohexylene; and a polymeric block (B) which is the reaction product of an aromatic dicarboxylic acid or a cycloaliphatic acid, and a short chain aliphatic or cycloaliphatic diol, having the formula

wherein R_1 is a straight or branched chain alkyl group of from about 2 to 10 carbon atoms or a cyclic group having the formula



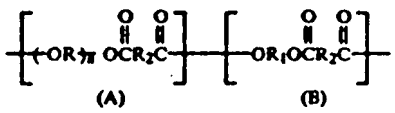
and R_2 is 1,4-phenylene of cyclohexylene: and the block (B) comprising from about 30% to 95% of the copolymer. The copolymer has a number average molecular weight of from about 25,000 to 39,000. The suture or ligature has good flexibility, yood fatigue life and a high tensile strength. The surgical suture package wherein R in the copolymer is butylene is preferred.

DESCRIPTION OF THE INVENTION

These sutures combine the advantages of a braided suture material (i.e., flexibility and knot security) and those of a monofilament suture material (i.e., smooth surface, low tissue drag, inertness, and ease of knot run down). Specifically, these sutures are non-absorbable

monofilament sutures which combine flexibility fatigue life, and high tensile strength.

The structures of the block copolymers of this invention may be represented by the following general formula:



wherein R and R_1 are the same or different straight or branched chain alkyl groups of 2 to 10 carbon atoms; R_2 is selected from the group comprising phenylene and cyclohexylene; and n is the number of repeating units.

In the polymeric block A, for example, polyethylene oxide or polybutylene oxide may constitute the soft segment of the block copolymer.

In the polymeric block B, for example, polyethylene terephthalate or polybutylene terephthalate may constitute the hard segment of the block copolymer.

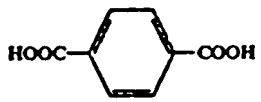
In order to have the desired qualities of flexibility and high tensile strength, the sutures of this invention must be formed from a copolymeric mixture of blocks A and B, wherein the hard segment B constitutes 30–95% of the mixture. Preferably, the B component should constitute 50–85% of the mixture.

Generally, the soft segment A is derived from a (tetramethylene ether)glycol having a number average molecular weight in the range of about 500-3000 may be used. The total number average molecular weight of the block polyether-esters is about 25–30,000.

The hard segment B can be derived from

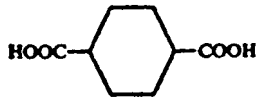
(1) a diacid, for example,

(a) terephthalic acid,



or,

(b) 1,4-cyclohexane dicarboxylic acid, or

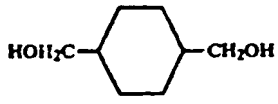


(c) from the dimethyl esters of these acids; and,

(2) a short chain glycol, for example,

(a) a linear or branched chain glycol of 2 to 10 carbon atoms; and preferably of 4 carbon atoms, or,

(b) 1,4-cyclohexanedimethanol,



or,

(c) 1,4-bis(hydroxymethyl)benzene

The reaction product of (1) and (2) forms the hard segment B.

The methods for preparing these block copolymers are known in the art. See, e.g., Great Britain Patent,

1,458,341 published Dec. 15, 1976; U.S. Pat. No. 3,763,109 issued Oct. 2, 1973; and U.S. Pat. No. 3,766,146 issued Oct. 16, 1973 which are incorporated herein by reference.

Sutures formed from the block copolymers described in this application, when extruded and drawn from 5X to 10X (where X is the original length of the undrawn strand), preferably from 6X to 8X, have the desired qualities of flexibility, fatigue life, tensile strength, knot security, smooth surface, low tissue drag, inertness and ease of knot run down.

The sutures formed from the block copolymers in accordance with this invention can be sterilized by a variety of methods recognized in the art including exposure to a gaseous sterilizing agent such as ethylene oxide, and exposure to radiation of gamma rays. Generally, the sutures of this invention cannot be sterilized by exposure to heat because the flexible properties of the sutures may be effected.

The sutures of this invention can be colored by mechanically blending with a pigment. Pigments such as titanium dioxide, iron oxide or carbon black give identifiable colors. Other colored pigments which do not cause deleterious tissue reactions may also be used to impart color to the strands. Other colored pigments which may also be used are disclosed in U.S. Pat. Nos. 3,636,956; 3,297,033 and 2,909,177 and British Pat. No. 1,375,008. These patents are incorporated herein by reference.

The sutures formed from the block copolymers of this invention were tested for toxicity by placing two 4cm. segments on each of three plates of HEp-2 cell culture. The cultures were incubated for 24 hours at 36° C., stained with crystal violet and checked for degeneration of the cell monolayer in the area of the suture segment. None of the suture segments showed any evidence of cytotoxicity.

The sutures were also treated in mice by the Systemic Injection Test according to the U.S.P. Biological Test for Plastic Containers No. 19. The sutures were subjected to an extraction procedure and the extractant was injected into mice. No adverse reactions were observed in any of the test animals.

For use as sutures, any size may be used, depending upon the preference of the surgeon. In the United States the more common standard sizes are the United States Pharmacopeia, which is abbreviated U.S.P., sizes (United States Pharmacopeia Convention, Inc., Mack Publishing Co., Easton, Pa.).

U.S.P. Size	U.S.P. Diameter (inches max.)
6-0	0.004
5-0	0.006
4-0	0.008
3-0	0.010

-continued

U.S.P. Size	U.S.P. Diameter (inches max.)
00	0.013
0	0.016

The results of tests conducted to compare three types of non-absorbable sutures: (1) Dermalon ®, a nylon suture American Cyanamid Company, Wayne, N.J.; and (2) Surgilene ®, a polypropylene suture of American Cyanamid Company, Wayne, N.J.; and (3) the copolymers of this invention are disclosed in the following examples.

EXAMPLE 1

A copolyester composed of a polytetramethylene oxide soft segment (MW = 1000) and a poly(tetramethylene terephthalate) hard segment and containing 58±2% of the hard segment is extruded at 230°–245° C. with a collection of extrudate at about 25 feet per minute. A two stage draw was used with an 8X draw at 160° C. in zone 1 and 1.1X draw at 120° C. in zone 2 for a total draw of 8.8X. The properties of this size 3/0 USP fiber (0.245mm) are described in the Table I below.

EXAMPLE 2

A copolyester composed of the hard and soft segments of Example 1 but at a ratio of 76% hard segment is extruded at 230°–245° C. A two stage draw is used where zone 1 is at 165° C. and drawn 2X and zone 2 is drawn 3.5X at 150° C. for a total draw of 7.0X. The properties of this size 3/0 U.S.P. fiber (0.231mm) are described in the Table I below.

TABLE I

	STRAIGHT PULL[1]	KNOT PULL[1]	FLEXUAL MODULUS[2]	FLEXUAL FATIGUE[3]	ELONGATION AT BREAK	TENACITY[4]
Example 1 Copolymer	75,256	41,055	0.54×10^5	12,972	53%	4.6
Example 2 Copolymer	80,049	38,485	1.31×10^5	6,665	36%	4.6
Dermalon ®	70,200	49,400	6.45×10^5	519	37%	4.2
Surgilene ®	64,000	45,000	9.98×10^5	807	24%	5.3

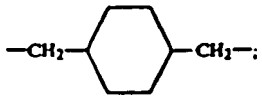
[1]pounds per square inch, ASTM D2256
[2]pounds per square inch, ASTM D790
[3]Cycles to failure, Folding Endurance Tester, Tinius Olsen Co.
[4]Grms./Denier, ASTM D2256

We claim:

1. A non-absorbable monofilament sterile surgical suture or ligature having an attached needle comprising a polymeric block (A) consisting of a polyalkylene ether of the formula

having a number average molecular weight of from about 500–3000 wherein R is a straight or branched chain alkyl group of from about 2 to 10 carbon atoms and R_2 is 1,4-phenylene or cyclohexylene and n is the number of repeating units and is defined by R and R_2, by R_1 in polymeric block (B), and by the total molecular weight of the copolymer; and a polymeric block (B) which is the reaction product of an aromatic dicarboxylic acid or a cycloaliphatic acid, and a short chain aliphatic or cycloaliphatic diol, having the formula

wherein R_1 is a straight or branched chain alkyl group of from about 2 to 10 carbon atoms or a cyclic group having the formula



and R_2 is 1,4-phenylene or cyclohexylene, said block (B) comprising from about 30% to 95% of said copolymer, and said copolymer having a number average molecular weight of from about 25,000 to 30,000, such that said

suture has good flexibility, good fatigue life and high tensile strength.

2. The surgical suture or ligature of claim 1, wherein the polymeric block (B) comprises from about 50% to 85% of the copolymer.

3. The surgical suture or ligature of claim 1, wherein the polymeric block (B) comprises from about 55% to 80% of the copolymer.

4. The surgical suture or ligature of claim 1, wherein R is selected from the group consisting of ethylene, propylene or butylene.

5. The surgical suture or ligature of claim 4, wherein R is butylene.

6. A surgical suture package comprising a sterile enclosure and therein a non-absorbable monofilament sterile surgical suture or ligature of claim 6.

7. The surgical suture package of claim 6 wherein R is butylene.

* * * * *

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 4,224,946 Dated September 30, 1980

Inventor(s) Donald Samuel Kaplan

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In Claim 6, column 8 line 16 delete "6" and add -1-.

Signed and Sealed this

Thirty-first Day of *March 1981*

[SEAL]

Attest:

RENE D. TEGTMEYER

Attesting Officer

Acting Commissioner of Patents and Trademarks

APPENDIX D

DEVICE CHARACTERISTICS

NOVAFIL™, Polybutester, Sterile, Monofilament, Synthetic, Nonabsorbable Suture* is manufactured from a thermoplastic polyester elastomer. The polybutester polymer is made into suture filaments as cited in Section XI of this submission. The suture is used in surgery wherever the use of a nonabsorbable monofilament suture or ligature is indicated.

The source and preparation of the suture follows:

Chemical Name	Common Name or Trade Name or Other Designations	Manufacturer
Polymer of polytetramethylene glycol with terephthalic acid and 1,4-butanediol	HYTREL® HTR-5721 Polymer XM-72 Polymer Polybutester Polymer	E.I.duPont de Nemours & Co., Inc. Polymer Products Dept. Wilmington,Del. 19898
[Phthalocyaninato (2-)]Copper	Copper Phthalocyanine	American Cyanamid Co. Organic Chemicals Div. Bound Brook,N.J.08805 or alternate source

*During the development phase, NOVAFIL™ suture was identified as XM-72 suture, and the terms are used interchangeably.

HYTREL® - Tradename of E.I. duPont de Nemours & Co., Inc.

HYTREL® HTR-5721, a polymer of polytetramethylene glycol with terephthalic acid and 1,4-butanediol, is as shown in the attached chemical structure. It contains two types of additives: an antioxidant system (*Irganox 1098 & 1019) at a level not to exceed 0.3%; and a tetrabutyl titanate catalyst at a level not to exceed 0.2%.

Copper Phthalocyanine, a certifiable pigment, which meets monograph specifications cited in 21CFR 74.3045, is typically prepared as cited in "Handbook of U.S. Colorants for Foods, Drugs and Cosmetics", p. 73, Daniel M. Marmion, John Wiley & Sons, 1979 (copy attached).

Certified copper phthalocyanine pigment is presently authorized for use in polypropylene sutures. DAVIS + GECK has filed Color Additive Petition 4C0181 to amend the regulations to allow the use of the pigment in NOVAFIL™ sutures. DAVIS + GECK has a supply of certified pigment for this purpose. A copy of the certificate is attached to this section.

All relevant suture specifications are listed in Section XI, Manufacturing/Controls, of this submission.

*Irganox 1019:

N,N-HEXAMETHYLENEBIS(3,5-DI-tert-BUTYL-4-HYDROXYHYDROCINNAMAMIDE)

Irganox 1098:

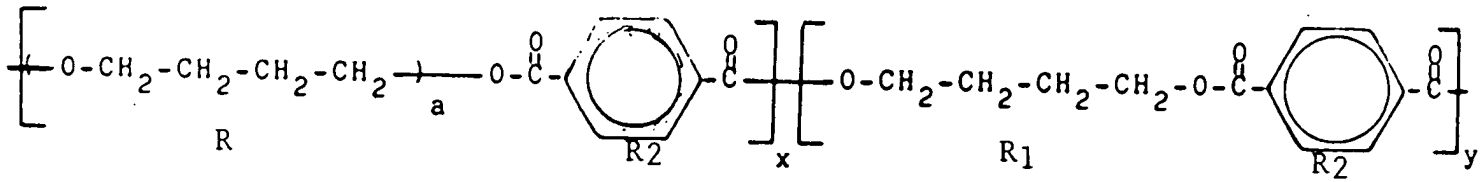
N,N-TRIMETHYLENEBIS(3,5-DI-tert-BUTYL-4-HYDROXYHYDROCINNAMAMIDE)

Figure 1

HYTREL® 5721

Synonyms: NOVAFIL polybutester, XM-72

Chemical Structure:



polytetramethylene glycol terephthalate — polybutylene terephthalate

A. Comparison with U.S. patent 4,224,946, claims 1 to 5 and 7:

1. x = polymeric block (A) = about 16% of the copolymer
   a = at least 2
   R = 4 carbon atoms
   R_2 = 1,4-phenylene
2. y = polymeric block (B) = about 84 % of the copolymer
   R_1 = 4 carbon atoms
3. x + y = 25,000 to 30,000 number average molecular weight

B. The identification of Hytrel® 5721 is contained in the attached American Cyanamid Company December 11, 1984 memorandum.

To:

Date: December 11, 1984

Location: Danbury R&D

to:

From:

Location: Danbury R&D

J. F. Schaefer

Extension:

Subject: Polyetherester Sutures

Reference:

4GT is polybutylene terephthalate; PTMEG is polytetramethylene ether glycol).

Molecular weight determinations

a number-average molecular weight

Duplicate measurements on HYTREL grade HTR-5721 gave 27,700 and 31,100,

HYTREL 7246 (now designated HYTREL 5721), for NOVAFIL™.

HYTREL 7246 consists of approximately 84%/16% 4GT/PTMEG.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

SEP 30 1985

Re: P840041
NOVAFIL® Monofilament Polybutester Suture, Nonabsorbable Surgical Suture, U.S.P. (Clear or Blue)
Filed: September 17, 1984
Amended: October 16, November 5, and 15, December 4, 1984; January 16, February 20, April 18 and 19, September 4, 26, and 30, 1985

John F. Schaefer, Ph.D.
Director, Regulatory Affairs
Davis and Geck
American Cyanamid Plaza
One Cyanamid Plaza
Wayne, New Jersey 07470

Dear Dr. Schaefer:

Sterile packages are available in USP sizes 10/0 through 02 (metric size 0.2-5) for blue sutures, 7/0 through 02 (metric size 0.5-5) for clear. NOVAFIL® is available either non-needled or affixed to the various Davis and Geck ATRAUMATIC® and D-TACH® needles. The PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin production and marketing of the device upon receipt of this letter.

Sincerely yours,

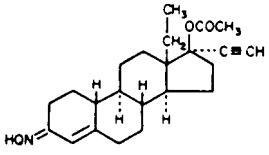
Kshitij Mohan

Kshitij Mohan, Ph.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

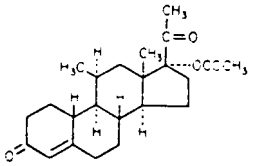
Enclosure

Norflurane *[1967]* (nor flure' ane). $C_2H_2F_4$. 102.03. (1) Ethane, 1,1,1,2-tetrafluoro-; (2) 1,1,1,2-Tetrafluoroethane. *CAS-811-97-2.* INN. *Anesthetic (inhalation).* (Merrell Dow†)

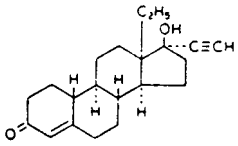
Norgestimate *[1975]* (nor jess' ti mate). $C_{23}H_{31}NO_3$. 369.50. (1) 18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)- (+)-; (2) (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester). *CAS-35189-28-7.* INN; BAN. *Progestin. [Name previously used: Dexnorgestrel Acetime.]* ✦*ORF 10131*



Norgestomet *[1974]* (nor jess' toe met). $C_{23}H_{32}O_4$. 372.50. (1) 19-Norpregn-4-ene-3,20-dione, 17-(acetyloxy)-11-methyl-, (11β)-; (2) 17-Hydroxy-11β-methyl-19-norpregn-4-ene-3,20-dione acetate. *CAS-25092-41-5.* INN. *Progestin.* (Searle) ✦*SC-21009*



Norgestrel *[1966]* (nor jess' trel). **USP**. $C_{21}H_{28}O_2$. 312.45. (1) 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(±)-; (2) (±)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one. *CAS-6533-00-2.* INN. *Progestin.* Microlut (Schering A.G., W. Berlin); Ovrette (Wyeth); component of Lo/Ovral (Wyeth); component of Ovral (Wyeth) ✦*Wy-3707*



Noriday. Syntex brand of combination product; *See* Norethindrone.

Norinyl. Syntex brand of combination product; *See* Mestranol; Norethindrone.

Norisodrine Aerotrol. Abbott brand of Isoproterenol Hydrochloride.

Norisodrine Sulfate. Abbott brand of Isoproterenol Sulfate.

Norlestrin. Parke-Davis brand of combination product; *See* Ethinyl Estradiol; Norethindrone Acetate.

Norlutate. Parke-Davis brand of Norethindrone Acetate.

Norlutin. Parke-Davis brand of Norethindrone.

Normodyne. Schering-Plough brand of Labetalol Hydrochloride.

Norpace. Searle brand of Disopyramide Phosphate.

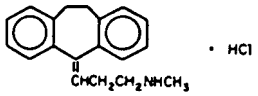
Norpramin. Merrell Dow brand of Desipramine Hydrochloride.

Nor-Q.D. Syntex brand of Norethindrone.

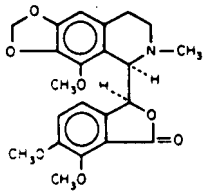
Norquen. Syntex† brand of combination product; *See* Mestranol.

Nortestosterone Phenylpropionate (NFN) — *See* Nandrolone Phenpropionate.

Nortriptyline Hydrochloride *[1963]* (nor trip' ti leen). **USP**. $C_{19}H_{21}N.HCl$. 299.84. (1) 1-Propanamine, 3-(10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-ylidene)-*N*-methyl-, hydrochloride; (2) 10,11-Dihydro-*N*-methyl-5*H*-dibenzo[*a,d*]cycloheptene-Δ^5,γ-propylamine hydrochloride. *CAS-894-71-3; CAS-72-69-5* [nortriptyline]. INN. *Antidepressant.* Aventyl Hydrochloride (Lilly); Pamelor (Sandoz) ✦*38489*

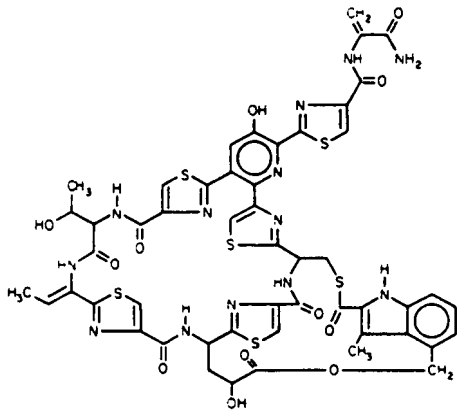


Noscapine (noss' ka peen). **USP**. $C_{22}H_{23}NO_7$. 413.43. (1) 1(3*H*)-Isobenzofuranone, 6,7-dimethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]-isoquinolin-5-yl), [*S*-(*R**,*S**)]-; (2) Narcotine. *CAS-128-62-1.* INN. *Antitussive.* Tusscapine (Fisons†) ✦*NSC-5366*



Noscosed. Alcon† brand of Chlorpheniramine Maleate.

Nosiheptide *[1978]* (noe si hep' tide). $C_{51}H_{43}N_{13}O_{12}S_6$. 1222.34. (1) Nosiheptide; (2) *N*-[1-(Aminocarbonyl)ethenyl]-2-[14-ethylidene-9,10,11,12,13,-14,19,20,21,22,23,24,26,33,35,36-hexadecahydro-3,23-dihydroxy-11-(1-hydroxyethyl)-31-methyl-9,12,19,24,33,43-hexaoxo-30,32-imino-8,5:18,15:40,37-trinitrilo-21,36-([2,4]-*endo*-thiazolomethanimino)-5*H*,15*H*,37*H*-pyrido[3,2-*w*]-[2,11,21,27,31,7,14,17]benzoxatetrathiatriazacyclohexatriacontin-2-yl]-4-thiazolecarboxamide. *CAS-56377-79-8.* INN. *Growth stimulant (veterinary).* Primofax (Hess & Clark†); (Rhone-Poulenc, France) ✦*RP 9671*



Novafed. Merrell Dow brand of Pseudoephedrine Hydrochloride.

✓ Novafil. Davis & Geck brand of Polybutester.

Novahistine. Merrell Dow brand of combination product; *See* Chlorpheniramine Maleate; Phenylephrine Hydrochloride.

Novaldin. Sterling brand of Dipyrone.

Novastat. Salsbury† brand of combination product; *See* Aklomide; Sulfanitran.

	Physical Form	Average Molecular Weight	Average Values			BASF Wyandotte Brand Name
			a	*b*	*c*	
212	liquid	2750	8	35	8	L 72
215	paste	4150	24	35	24	P 75
217	solid	6600	52	35	52	F 77
181	liquid	2000	3	30	3	L 61
182	liquid	2500	8	30	8	L 62
183	liquid	2650	10	30	10	L 63
184	liquid	2900	13	30	13	L 64
185	paste	3400	19	30	19	P 65
122	liquid	1630	5	21	5	L 42
123	liquid	1850	7	21	7	L 43
124	liquid	2200	11	21	11	L 44
101	liquid	1100	2	16	2	L 31
105	liquid	1900	11	16	11	L 35
108	solid	5000	46	16	46	F 38

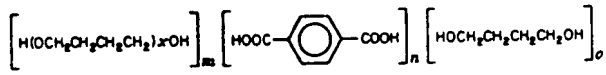
Poloxamer 182LF *[1973].* Liquid nonionic surfactant of the poly(oxypropylene)poly(oxyethylene) copolymer type. The average molecular weight is 2450. (In the graphic formula, which is portrayed the same as for Poloxalene, average values are: $a = 7$; $b = 30$; $c = 7$.) (1) Oxirane, methyl-, polymer with oxirane; (2) Polyethylene-polypropylene glycol; (3) α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) (27–31 moles)poly(oxyethylene) block copolymer. *CAS-9003-11-6. Food additive; pharmaceutic aid.* Pluronic L-62LF (BASF Wyandotte)

Poloxamer 188 *[1975].* Waxy, nonionic surfactant of the poly(oxypropylene)poly(oxyethylene)copolymer type. The average molecular weight is 8350. (In the graphic formula, which is portrayed the same as for Poloxalene, average values are: $a = 75$; $b = 30$; $c = 75$.) (1) Oxirane, methyl-, polymer with oxirane; (2) Polyethylene-propylene glycol; (3) α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) (27–31 moles)poly(oxyethylene) block copolymer. *CAS-9003-11-6. Laxative.* Pluronic F-68 (BASF Wyandotte); Polykol (Upjohn†); component of Casakol (Upjohn†) *[Name previously used: Poloxalkol.]*

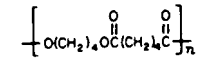
Poloxamer 188 LF *[1979].* Prilled solid nonionic surfactant of the poly(oxypropylene)poly(oxyethylene) copolymer type. The average molecular weight is 7700. (In the graphic formula, which is portrayed the same as for Poloxalene, average values are: $a = 68$; $b = 30$; $c = 68$.) (1) Oxirane, methyl-, polymer with oxirane; (2) Polyethylene-polypropylene glycol; (3) α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block polymer. *CAS-9003-11-6. Pharmaceutic aid (surfactant).* Pluronic F68LF (BASF Wyandotte)

Poloxamer 331 *[1971].* Liquid nonionic surfactant. The average molecular weight is 3800. (In the graphic formula, which is portrayed the same as for Poloxalene, average values are: $a = 7$; $b = 54$; $c = 7$.) (1) Oxirane, methyl-, polymer with oxirane; (2) Polyethylene-polypropylene glycol; (3) α-Hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene) 53–59 (moles)-poly(oxyethylene) block copolymer. *CAS-9003-11-6. Food additive.* Pluronic L-101 (BASF Wyandotte)

Polybutester *[1985]* (pol'i bute es ter). $[(C_4H_8O)xH_2O]_m(C_8H_6O_4)_n(C_4H_{10}O_2)_o$. (1) Poly(oxy-1,4-butanediyl), α-hydro-ω-hydroxy-, polymer with 1,4-benzenedicarboxylic acid and 1,4-butanediol; (2) Polytetramethylene glycol, polymer with terephthalic acid and 1,4-butanediol. *CAS-37282-12-5. Surgical aid (surgical suture material).* Novafil (Davis & Geck) ✦*XM-72*



Polybutilate *[1976]* (pol i byoo' ti late). $(C_{10}H_{16}O_4)_n$. (1) Poly[oxy-1,4-butanediyloxy(1,6-dioxo-1,6-hexanediyl)]; (2) Poly(oxytetramethyleneoxyadipoyl). *CAS-24936-97-8. Surgical aid (surgical suture coating).* (Ethicon)



Polycillin. Bristol brand of Ampicillin.

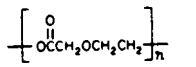
Polycillin-N. Bristol brand of Ampicillin Sodium.

POLYCON II. Syntex Ophthalmics brand of Silafocon A.

Polycycline Hydrochloride. Bristol-Myers brand of Tetracycline Hydrochloride.

Polydextrose *[1979]* (pol ee dex' trose). A randomly bonded glucose polymer with some sorbitol end-groups, and with citric acid residues attached to the polymer by mono- or diester bonds. The 1→6 bond predominates, but all possible bonds are present in the molecule. Molecular weight: average of 1500, with upper limit of 20,000. (1) Polydextrose; (2) D-Glucose polymer, reaction product with citric acid and sorbitol. *CAS-68424-04-4. Food additive.* (Pfizer) ✦*CP-31,081*

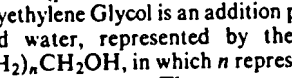
Polydioxanone *[1978]* (pol ee dye ox' a none). $(C_4H_6O_3)_n$. (1) Poly[oxy(1-oxo-1,2-ethanediyl)oxy-1,2-ethanediyl]; (2) Poly(oxycarbonylmethyleneoxyethylene). *CAS-31621-87-1. Surgical aid (surgical suture material, absorbable).* PDS (Ethicon)



Polyelectrolyte 211 — *See* Sodium Alginate.

Polyetadene (INN) — *See* Polyethadene.

Polyethadene *[1964]* (pol ee eth' a deen). $(C_4H_6O_2)_m(C_2H_5N)_n$. [Polyetadene is INN.] (1) 2,2'-Bioxirane polymer with aziridine; (2) 1,2:3,4-Diepoxybutane polymer with ethylenimine. *CAS-9003-23-0. Antacid.* (Lilly†) ✦*30639*



Polyethylene Glycol (pol ee eth' i leen). NF. $H(OCH_2CH_2)_nOH$. Polyethylene Glycol is an addition polymer of ethylene oxide and water, represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, in which *n* represents the average number of oxyethylene groups. The average molecular weight is not less than 95.0 percent and not more than 105.0 percent of the labeled nominal value if the labeled nominal value is below 1000; it is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value if the labeled nominal value is between 1000 and 7000; it is not less than 87.5 percent and not more than 112.5 percent of the labeled nominal value if the labeled nominal value is above 7000. (1) Poly(oxy-1,2-ethanediyl, α-hydro-ω-hydroxy-; (2) Polyethylene glycol. *CAS-25322-68-3. Pharmaceutic aid (ointment base); pharmaceutic aid (suppository base); pharmaceutic aid (solvent); pharmaceutic aid (tablet excipient); pharmaceutic aid (tablet and/or capsule lubricant).* Atpeg 300 (ICI Americas); Atpeg 400 (ICI Americas); Atpeg 600 (ICI Americas); Carbowax Sentry (Union Carbide) *[Note—A number of forms of polyethylene glycol have been consolidated under a composite monograph in NF.]*

Polyferose *[1962]* (pol i fer' ose). A chelate complex of iron and a polymerized derivative of sucrose. (1) β-D-Fructofuranosyl α-D-glucopyranoside deriv., polymer, iron complex; (2) Carbohydrates, compounds, iron complex. *CAS-9009-29-4. Hematinic.* Jefron (Merrell Dow†)

Polyflex [Veterinary]. Bristol brand of combination product; *See* Ampicillin.

Polyglactin 370 *[1978]* (pol ee glak' tin). $(C_6H_8O_4)_m(C_4H_4O_4)_n$. (1) 1,4-Dioxane-2,5-dione, 3,6-dimethyl-, polymer

† Brand name formerly used, and/or firm no longer concerned with this product.

The authorized list of established names for drugs in the United States of America

USAN *and the USP dictionary of drug names*

A compilation of the United States Adopted Names (USAN) selected and released from June 15, 1961, through June 15, 1985, and current USP and NF names for drugs (main list), with two appendixes of other drug names

All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the main list of names in this volume as being the established names in accordance with the Federal Food, Drug, and Cosmetic Act. [*See 49 Fed. Reg. 37575 (1984) amending 21 CFR § 299.4.*]

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William M. Heller, Ph.D., *Executive Director*

12601 Twinbrook Parkway, Rockville, Md. 20852

Library of Congress Catalog Card Number 72-88571

ISSN 0090-6816

ISBN 0-913595-12-8

Printed by Mack Printing Company, Easton, Pennsylvania 18042

E. Summary of Studies

Physical Properties and Retention of Tensile Strength

NOVAFIL™ met USP XX requirements for diameter, needle-pull and knot-pull breaking strengths. NOVAFIL™ maintained its tensile strength after two years in a simulated physiological environment, and after four months subcutaneous implantation in rats and rabbits.

Experimental Surgery

NOVAFIL™ exhibited an excellent profile of repair efficacy, knot security and suture integrity in various surgical procedures including aortic graft, auriculotomy, thoractomy and general skin closure in dogs; microvascular repair of small vessels in rats; and corneoscleral repair in rabbits. In all of these studies, tissue response to NOVAFIL™ was mild and transient, and normal wound healing occurred.

Toxicology

In all toxicology studies, adequate multiples of the maximum intended human exposure to NOVAFIL™ were implanted or extracts of the suture material further exaggerating exposure to potentially leachable components were administered. In acute studies, no signs of systemic or local toxicity attributable to NOVAFIL™ occurred after two weeks implantation in rats and dogs or after single doses of extracts to mice.

In subchronic and chronic toxicity studies in rats and dogs in which NOVAFIL™ was implanted for periods up to six months or extracts of NOVAFIL™ were administered daily for one month, there were no changes indicative of a systemic toxicologic effect. There was no evidence of oncogenic potential following lifetime implantation of NOVAFIL™ in rats.

Extensive testing of NOVAFIL™ and/or extracts of the suture showed no evidence of mutagenic potential. NOVAFIL™ sutures implanted in mice at various intervals up to four months did not increase the number of mononuclei in polychromatic erythrocytes. In vitro, NOVAFIL™ and extracts of the suture material produced negative results in microbial mutagenicity (Ames) tests and mutation assays in mouse lymphoma cells, unscheduled DNA synthesis tests in primary rat hepatocytes and transformation assays in mouse embryo cells.

There were no teratogenic effects after subcutaneous implantation of NOVAFIL™ in rats or rabbits during the period of organogenesis.

NOVAFIL™ did not evoke an immediate or delayed antigenic response in guinea pigs sensitized by one month implantation of the suture and challenged two weeks later. Extracts of NOVAFIL™ did not exhibit pyrogenic or local irritation potential in rabbits. In vitro, NOVAFIL™ sutures were not hemolytic to human erythrocytes and were not cytotoxic to mouse fibroblast cells.

Interaction with Infection

NOVAFIL™ did not enhance aerobic infection in a model in which rats were inoculated with either Staphylococcus aureus or Pseudomonas aeruginosa, and bacterial counts were measured four and seven days later. In vitro, NOVAFIL™ did not exert biologically significant effects on aerobic (Staphylococcus aureus or Pseudomonas aeruginosa) or anaerobic (Peptostreptococcus anaerobius or Bacteroides fragilis) bacterial growth.

Biocompatibility (Local Tissue Response)

The biocompatability of NOVAFIL™, based on gross and/or microscopic examinations of the site of implantation, was assessed in toxicology and experimental surgery studies in rats, rabbits and dogs. The local response of cutaneous, subcutaneous, cardiac, vascular, muscle and opthalmic tissues to NOVAFIL™ was evaluated at intervals ranging from two days to two years and, in most cases, compared to reference sutures. In all of these cases, normal wound healing occurred. The local tissue reaction to NOVAFIL™ was minimal, and was generally similar across species and in different tissues. Microscopically, the expected tissue response to an innocuous nonabsorbable material occurred after NOVAFIL™ implantation. The response was sequential and was characterized initially by a slight transient infiltration of neutrophils which persisted for about seven days. It was followed by a mild infiltration of mononuclear phagocytes and fibroblasts which gradually resolved within three to six months. By seven days, a fibrous connective tissue capsule (one to two cells thick) began to form around NOVAFIL™; the capsule was thickest (three to four cells) at 14 days and decreased in thickness (one to two cells) beginning at 21 days and persisting at the remaining intervals

throughout lifetime implantation. All of these findings, which were comparable to those observed after implantation of reference sutures, represent the expected local tissue response to a nonabsorbable suture. In all experiments, the suture matrix remained intact, and there was no evidence of leaching of the pigment.

F. Clinical Studies

The safety and efficacy of NOVAFIL™, a nonabsorbable suture, was evaluated in randomized, controlled studies of 558 patients (288 NOVAFIL™, 270 control) undergoing general and vascular surgery (226 NOVAFIL™, 210 control) microsurgery (9 NOVAFIL™, 7 control), and ophthalmic surgery (53 NOVAFIL™, 53 control).

RESULTS: GENERAL AND VASCULAR SURGERY AND MICROSURGERY PROTOCOLS

NOVAFIL™ was comparable to the control suture (principally polypropylene) for the extent of healing, inflammation, and drainage in sutured skin, and with regard to other parameters used to determine safety and efficacy including types of operative procedures, use in tissues, complete wound healing, and patency of anastomosed blood vessels. There were no postoperative complications, deaths, changes in laboratory parameters, or adverse effects reported that were related to the suture.

A total of 226 NOVAFIL™ and 211 control patients completed the study. Among the numerous diagnoses recorded for patients in the general and vascular surgery protocol, the most common were inguinal hernia (39), occluded artery (39), arteriosclerosis (29), abdominal aortic aneurysm (22), carotid artery sclerosis (20), cholelithiasis (19), vascular occlusion (18), and hypomastia (17). The most common diagnoses in the microsurgery protocol were finger amputation (5), finger avulsion (2), and crush injuries of fingers (2). Diabetes mellitis (36), hypertension (32), and heart disease (29) were the three most frequently listed coexistent diseases.

The operative site was clean for most patients (207 NOVAFIL™, 190 control) and no suture-related complications occurred during surgery. Skin, fascia, muscle, subcutaneous, parietal peritoneum, gastrointestinal tract, blood vessel, and nerve were the tissues sutures. Skin sutures were removed in less than 14 days for 77% of NOVAFIL™ patients and 87% of control patients. Wound healing was judged to be complete in more than 95% of patients in both suture groups, and 75% of all patients had complete wound healing in less than four weeks. Wound healing was judged to be partial in patients who were either lost to follow-up, died before wound healing was complete, or required reoperation for their disease. Blood vessel patency and nerve regeneration were evaluated in a small number of patients (6 NOVAFIL™, 7 control) who had microsurgery performed.

RESULTS: OPHTHALMIC SURGERY PROTOCOL

NOVAFIL™ was comparable to the control suture for the extent of healing and time to healing of corneoscleral wounds and wounds of the iris. One hundred patients (50 NOVAFIL™, 50 control) were assessed for efficacy in the ophthalmic surgery protocol. Polypropylene and nylon (25 patients each) were the predominant control sutures; DEXON® was used as the control suture in six patients not included in the efficacy analysis. All patients were diagnosed as having a cataract and the most frequent coexistent diseases were glaucoma (9) and diabetes mellitis (6).

NOVAFIL™ and control sutures were used in an equal number of sites (56), and in two tissues, corneal and scleral. There were no suture-related complications during surgery. No patient developed edema or infection, and only three patients (2 NOVAFIL™, 1 control) developed minimal inflammation in corneoscleral wounds. There was no edema, inflammation, or infection reported in wounds of the iris. All patients were followed postoperatively for a minimum of four months, and all patients in both suture groups demonstrated complete healing of corneoscleral wounds and wounds of the iris at their final evaluation. By the eighth postoperative week, 86% of NOVAFIL™ patients and 94% of control patients had complete healing of corneoscleral wounds, and all but one NOVAFIL™ patient had complete healing of wounds of the iris.

There were no postoperative complications or adverse effects reported that were related to the sutures, and there were no deaths during the study.

Conclusion

Clinical and preclinical information demonstrates NOVAFIL™ to be safe and efficacious for use in a variety of tissues and surgical procedures. The safety and efficacy is comparable to control sutures.

APPENDIX F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U. S. Patent: 4,224,946
Issued: September 30, 1980

Assignee: American Cyanamid Company
Inventor: DONALD SAMUEL KAPLAN

Group: 120

Serial No.: 933,224
Filed: August 14, 1978

Director:
Charles E. Van Horn

Title: SURGICAL SUTURES DERIVED FROM SEGMENTED POLYETHER-ESTER BLOCK COPOLYMERS

November 18, 1985

Hon. Commissioner of Patents
and Trademarks

Washington, D. C. 20231

S i r:

Declaration In Support Of
An Application For Extension
Of The Term Of U.S. Patent 4,224,946

The following is a declaration of JOHN J. HAGAN.

THAT I have a business address and telephone No. as follows:

1937 West Main Street, P.O. Box 60, Stamford, Connecticut 06904-0060, telephone No. (203) 348-7331;

THAT this declaration is in support of and filed with an application to extend the term of U.S. patent 4,224,946, (hereafter the '946 patent) as more fully identified in the above heading;

THAT I am the same John J. Hagan who is the manager of the Patent Law Department, American Cyanamid Company, Stamford, Connecticut 06904-0060;

THAT I have personal knowledge that the '946 patent is assigned to American Cyanamid Company;

THAT the filing date of the '946 patent is August 14, 1978;

THAT I have continuously been the manager of the assignee's Patent Law Department from at least August 14, 1978 to the present;

THAT I have reviewed and understand the contents of the application for extension of the '946 patent being submitted pursuant to 35 U.S. Code 156, Extension of Patent Term;

THAT I believe the'946 patent is entitled to an extension pursuant to 35 U.S. Code 156, and to the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156, part A, as published in 1047 OG 16-20 (1984);

THAT I believe an extension of 626 days (the length claimed in the '946 patent extension application) is fully justified under 35 U.S.C. 156;

THAT I believe the '946 patent meets the conditions for extension of the term of a patent as set forth in the GUIDELINES FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156, part B;

THAT I believe American Cyanamid Company is the owner of record of U.S. patent 4,224,946 as shown by an assignment recorded in the U.S. Patent and Trademark Office on frame 812, reel 3574, and therefore has the legal right to request this extension; and

THAT from a resolution by the assignee's Board of Directors, I have the authority to sign documents filed with the United States Patent and Trademark Office, which resolution is attached to and made a part of this declaration.

John J. Hagan

John J. Hagan
Registration No. 17,129

ST-52 11/79

CERTIFICATE

I, D. C. Droste, Assistant Secretary of American Cyanamid Company, a Maine corporation (the Company), hereby certify that the following is a complete and accurate copy of a resolution duly adopted by the Board of Directors of the Company at a regular meeting held on October 17, 1972, at which meeting a quorum was present and acting throughout, and that the same has not been rescinded or further amended and is now in full force and effect:

> RESOLVED: That any one of the Chairman of the Board, the President, the Vice Presidents, the Treasurer, the Assistant Treasurers, the Secretary, the Assistant Secretaries, the Manager of the Patent Law Department, and the Manager of the Trademark Law Department, be, and he hereby is, authorized, in the name and on behalf of this Company, to execute such powers of attorney and other documents, and to make such affidavits, as the person executing such documents or making such affidavits may deem to be necessary or desirable, from time to time, in connection with Letters Patent or trademark registrations, and applications for Letters Patent or trademark registrations, or in connection with any opposition, nullity, revocation, infringement or cancellation proceedings relating to Letters Patent or trademark registrations and to applications for Letters Patent or trademark registrations of other parties.

I FURTHER CERTIFY that J. J. Hagan is Manager of the Patent Law Department of this Company.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed the seal of this Company this 5th day of September, 1974.

Assistant Secretary